

Award Number: W81XWH-15-2-0088

TITLE: Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture

PRINCIPAL INVESTIGATOR: Dr. Jessica C. Rivera

CONTRACTING ORGANIZATION: The Geneva Foundation
Tacoma, WA 98402

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick,
Maryland 21702-5012

DISTRIBUTION STATEMENT:

X Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202- 4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) OCT 2016		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 30 Sep 2015-29 Sep 2016	
4. TITLE AND SUBTITLE Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-2-0088	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Jessica Rivera				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation 917 Pacific Ave., Ste. 600 Tacoma, WA 98402				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) US Army Medical Research and Materiel Command Ft Detrick, MD 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT <p>The objective of the proposed research is to develop new models for predicting the risk of post-traumatic osteoarthritis (PTOA) following intra-articular fracture (IAF). Aim 1, pursued this year, involved evaluating pre- and post-treatment CT data from patients with combat-related IAFs to measure fracture severity and post-reduction contact stress exposure. This study is being conducted in collaboration with the University of Iowa (PI: Donald Anderson, PhD) who is conducting these calculations on patients identified at the U.S. Army Institute of Surgical Research. IRB and HRPO approval has been obtained at both sites. Ongoing screening of potential subjects identified through the Department of Defense Trauma Registry has resulted in 58 subjects "enrolled." Of these 42 subjects' images have already been forwarded to U of Iowa for analysis.</p> <p>Our partners at the U of Iowa continue to work on related efforts in civilian trauma patients to refine the measuring techniques. The military subjects pose some unique challenges in terms of injury severity but we remain confident that our collaborator's skill in imaging analysis will remain successful as we study our military patients.</p>					
15. SUBJECT TERMS: Post-osteoarthritis, CT-based analysis, intra-articular fractures					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

<u>Table of Contents</u>	<u>Page</u>
Table of Contents	3
Introduction	4
Keywords	4
Accomplishments	4
Impact.....	6
Changes/Problems	6
Products.....	6
Participants & Other Collaborating Organizations	7
Special Reporting Requirements	7
Appendices	8

Introduction:

The objective of this research is to develop new models for predicting the risk of post-traumatic osteoarthritis (PTOA) following intra-articular fracture (IAF). Our collaborators at the University of Iowa previously developed capabilities to predict PTOA risk from acute fracture severity (measured from pre-op CT) and chronic elevated contact stress (post-op CT) associated with IAFs, but more patient data are needed to make the risk models clinically useful. Prospective studies of PTOA development following IAFs face many challenges. Severe IAFs are not frequently seen in civilian practice, making it difficult to accrue sufficient numbers for clinical study. An added challenge is that in order to determine if a patient develops PTOA, they may need to be followed for years into the future, threatening subject retention. One of the attractive features of the CT-based measures of mechanical factors pioneered by the Initiating PI (Anderson) is that retrospective studies can include patients who were injured years in the past. Recent military conflicts, which unfortunately produced a substantial number of severe fractures, including IAFs, provide a unique opportunity to overcome these challenges and to honor the military personnel who sustained combat-related IAFs. Given their prevalence and severity, and the degree to which these injuries impact long-term function of injured service members, better methods to predict PTOA risk would benefit our current generation of new veterans, as well as future service members at risk for IAF.

Keywords:

Post-traumatic osteoarthritis, CT analysis, intra-articular fractures

Accomplishments:

What were the major goals of the project?

The Statement of Work includes 6 major tasks over 3 Specific Aims:

Specific Aim 1: Evaluate pre- and post-treatment CT data from patients with combat-related IAFs to measure fracture severity and post-reduction contact stress exposure	
Major Task 1: Regulatory Approval	Months
Subtask 1.1: Obtain local IRB	1-3
Subtask 1.2: Obtain HRPO approval	4-6
<i>Milestone #1: Regulatory approval received</i>	5-6
Major Task 2: Adapt CT Analysis Methods	Months
Subtask 2.1: Obtain representative CT studies	3
Subtask 2.2: Trial analysis methods with CT studies	1-3
Subtask 2.3: Modify analysis methods as needed	3-9
<i>Milestone #2: Co-author manuscript on methods to analyze combat-related IAFs</i>	9-12
Major Task 3: Subject Identification	Months
Subtask 3.1: Obtain potential subject list with demographic and injury data from DoDTR	7
Subtask 3.2: Screen available CT scans for requisite images for inclusion	8-12
<i>Milestone #3: Subject list finalized</i>	12
Major Task 4: CT Calculations	Months
Subtask 4.1: De-identified CDs compiled and express mailed from Site 2 to Site 1	9-13
Subtask 4.2: CT calculations for injury severity and post-reduction contact stresses	10-18
<i>Milestone #4: Co-author manuscript on fracture severity and post-reduction contact stress measures in patients with combat-related IAFs</i>	18-24

Specific Aim 2: Measure the occurrence of PTOA up to ten years following fracture reduction surgery	
Major Task 5: PTOA radiographic frequency	Months
Subtask 5.1: Identify radiographs for KL grading; multiple investigators do KL grading	9-14
<i>Milestone #5: Co-author paper detailing PTOA incidence and grading for patients with combat-related IAFs</i>	16-20

Specific Aim 3: Quantify the extent to which fracture severity and post-reduction contact stress predict PTOA	
Major Task 6: PTOA symptoms and quality of life	Months
Subtask 6.1: Identify subjects' contact information through DoD and/or VA sources	12-16
Subtask 6.2: Conduct prospective contacting of subjects for outcomes questionnaires	12-28
<i>Milestone #6: Co-author manuscript detailing symptoms and treatment timelines for patients with combat-related IAFs</i>	25-32
Subtask 6.3: Correlate CT-based analysis results with KL grade/PTOA status, questionnaire outcomes, and various radiographic results	28-32
<i>Milestone #7: Co-author manuscript detailing relationships between CT-based results and PTOA outcomes – PTOA risk model</i>	32-36

What was accomplished under these goals?

Major Task 1 is completed (USAISR Protocol Number H-15-022, HRPO Log Number A-18857, IRB Protocol Number M-10466) as of October 2015.

Major Task 2 is underway. Our collaborators at the University of Iowa continue to refine the CT analysis methodology and have successfully disseminated their results in this work on civilian trauma subjects via two accepted manuscripts and one submitted abstract. This work will support the methods paper for the unique challenges posed by the CT analysis of military subjects.

Major Task 3 is underway. After receipt of the potential subject list by way of Department of Defense Trauma Registry (DoDTR) request, we immediately began screening subjects for inclusion and exclusion criteria. A total of 58 subjects have been identified for inclusion and are considered “enrolled.” Additional subjects continue to be screened.

Major Task 4 is underway. CDs containing CT imaging from enrolled subjects are being sent to U of Iowa once they are checked and confirmed to be de-identified. As the CT cases are received there, Dr. Anderson's lab is performing calculations of injury severity and post reduction contact stress. So far, the imaging data for 42 subjects have been forwarded to Iowa for analysis, with another 16 subjects identified and their imaging studies requested. Analysis of six cases are completed so far.

- CT studies (de-identified) transferred to Iowa for inspection --- 01-11-2015
- Additional CT studies transferred to Iowa for inspection and analysis --- 30-03-2016
- Fracture severity assessment completed on first subject in the study --- 08-06-2016

Major Task 5 is underway at our local site. As subjects are screened in, we are abstracting the DoD electronic medical record to examine the care received for the injured joint for as long as the subjects are seen within the DoD health care system.

Major Task 6 initial steps are currently being planned.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report. Specific abstract submission dates have been identified in the 2017 calendar year as planned targets as our data becomes available.

What do you plan to do during the next reporting period to accomplish the goals?

In the coming quarter, we will continue screening subjects and including those who meet study criteria. This will result in additional subjects' CT images being transferred to Dr. Anderson's lab for analysis. We will also continue data abstraction for Major Task 5 in the DoD electronic medical record. We are also planning a site visit for Dr. Anderson to visit SAMMC to facilitate planning of what tasks are pending towards our specific aims.

Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report; however, the end result of this project will contribute to discipline of PTOA prediction based on CT metrics.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

Changes/Problems

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We encountered a delay early in the 2016 calendar year with the process of obtaining the CDs for analysis. This was in part due to restrictions placed on CD burning as well as discovering that the initial process we planned for de-identifying images still contained information we felt should be removed prior to transferring the CT scans from our site to the U of Iowa. We solicited the help from our radiology informatics department to resolve these challenges. After carefully checking the first CDs made with their guidance, we confirmed the de-identified nature and were able finally begin sending the CT images to Dr. Anderson's lab.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Not applicable.

Products:

Publications, conference papers, and presentations

Nothing to report from this site directly from these data. Dr. Anderson's lab has had to publications accepted related to this work in civilian populations.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report from this site directly from these data. The CR analysis techniques previously described by Dr. Anderson will face specific required modifications as they are applied to military subjects due to the severity of the injury and multiple fractures typical of combat injuries.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Jessica Rivera
Project Role: PI
Nearest person month worked: 0.60
Contribution to Project: MAJ Rivera serves as the site study PI on this research project for the study's partnering PI option. She will provide the necessary programmatic leadership, administrative oversight and support for all aspects of the proposed work to be conducted at ISR/SAMMC site, ensuring that personnel and departmental resources are properly aligned to achieve the goals of this study. She meets with the study personnel and communicates with the partnering site on a regular basis to review planning and execution of the proposed project. Finally MAJ Rivera will be responsible for the preparation of technical reports, manuscripts, and other dissemination materials generated by this study.

Name: Allyson Corona
Project Role: Research Coordinator
Nearest person month worked: 6
Contribution to Project: Ms. Corona is responsible for the day-to-day operations of the study. She will be responsible for assisting compilation of radiographic images and chart abstraction. She will also assist with the preparation of all study related correspondence and technical reports, maintain research files and data, procure study supplies and coordinate all procurement requests through The Geneva Foundation, and ensure budgetary adherence.

Name: Stephanie DeLeon
Project Role: Research Coordinator
Nearest person month worked: 2.40
Contribution to Project: Ms. DeLeon is responsible for the day-to-day operations of the study. She will be responsible for assisting compilation of radiographic images and may assist with chart abstraction. She will also assist with the preparation of all study related correspondence and technical reports, maintain research files and data, procure study supplies and coordinate all procurement requests through The Geneva Foundation, and ensure budgetary adherence.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

Special Reporting Requirements

COLLABORATIVE AWARDS: The Collaborating PI at U of Iowa (Dr. Donald Anderson) is submitting a separate progress report for that site.

Appendices

Quad chart, updated 28SEP2016



Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture

W81XWH-15-2-0088

PI: Jessica Rivera, M.D.

Task Area: ETRM

Award Amount: \$240K

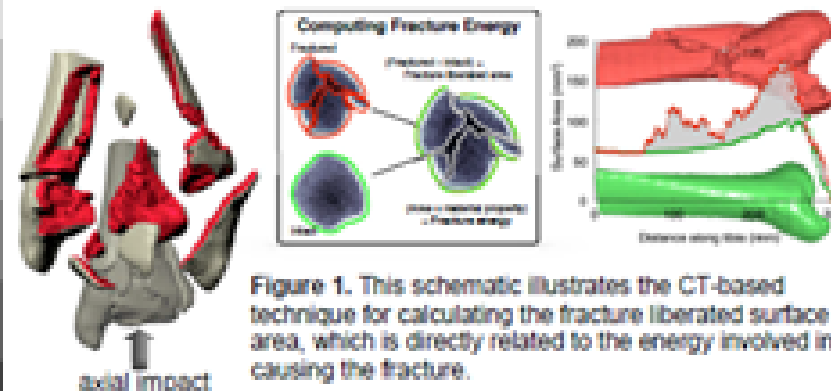


Study/Product Aim(s)

- Aim 1. Determine the proportion and timing of PTOA radiographic development in lower extremity IAFs following combat injury
- Aim 2. Evaluate pre- and post-treatment plain radiography and computed tomography (CT) data from IAF fracture patients to measure fracture severity and post-reduction contact stress.
- Aim 3. Measure the occurrence of PTOA up to ten years following fracture reduction surgery, and quantify the extent to which fracture severity and post-reduction contact stress predict PTOA.

Approach

Subjects identified by the DoDTR with lower extremity intra-articular fracture will be abstracted for the outcomes of PTOA development clinically and radiographically. Pre fixation and post fixation CT images will be shared with U of Iowa for fracture energy and contact stress calculations. These calculations will be tested for association with PTOA outcome.



Timeline and Cost

Activities	FY16	FY18	FY17	FY18
IRB approval				
Data Collection (local)				
Data Compilation (collaborator)				
Analysis and Dissemination				
Proposed Budget/Year	\$60	\$64	\$64	\$63
Expended Budget/Year	\$7	\$20.6	\$106	\$106

☐ Completed ☐ In Progress ☐ Pending

Goals/Milestones

CY18 Goal – Regulatory and Start up

- IRB and HRPO approval
- Hiring actions and CRADA with U of Iowa
- Begin protocol

CY17 Goals – Data Collection/Sharing

- Complete local data collection
- Compile CT metrics data from collaborative site (U of Iowa)

CY18 Goal –

- Continue patient recruitment and analysis
- Continue analyses to ascertain statistical power and to identify salient pathological outcomes

Comments/Challenges/Issues/Concerns

None

Budget Expenditure to Date

Total Proposed Expenditure: \$240K

Total Actual Expenditure: \$27K

Updated: (September 28, 2016)